REMARKS

Claim 63 is pending in the present application.

In reviewing the prosecution history of this application, Applicants noted that the Notice of Allowability mailed 26 Feb 2010 states the following as the Examiner's reason for allowance (underlining added):

> The instant application provides unexpected results that PLG (poly-L-glutamate) avoids flocculation induced by PRP and that the presence of PLG in Hib formulations reduces immune interference between PRP and Infanrix-Penta combinations (vaccine comprising multiple antigens). The specification teaches that Applicants have discovered that adding PLG to a vaccine comprising PRP and aluminium hydroxide allows for the PLG to compete with PRP thereby protecting it from any aluminium hydroxide present in the vaccine, e.g., by reducing the amount or rate of binding of PRP to adjuvant and/or the extent or rate of flocculation, yet surprisingly does not cause antigens already absorbed to aluminium hydroxide to become significantly desorbed.

Applicants further note that in some Office Actions (e.g., Final Office Action of 20 Aug 2009, page 6, line 15), the Examiner refers to PLG as "reducing the amount or rate of binding of PRP to adjuvant...."

The specification does state the theory that PLG prevents binding of PRP to adjuvant. However, applicants submit that this explanation of *how* PLG reduces immune interference is not material to patentability of claims to immunogenic compositions, in view of the specification and record as a whole, e.g., the immunogenicity data provided and the showing that PLG reduces flocculation (which can render a vaccine unusable).

(All paragraph numbers cited herein correspond to the published US Application 2006/0121059.)

Paragraph 0005 of the specification cites WO 97/00697 regarding the reduction in PRP antibody titres when a DTPa combination vaccine is extemporaneously mixed with unadjuvanted PRP conjugates, and cites WO 97/00697 regarding reduction of PRP antibody titres when PRP conjugate is adsorbed onto aluminium hydroxide. The specification then states that "(t)hese results indicated that

there was interference between the aluminium hydroxide of the DTPa vaccine and PRP."

At paragraph 0006 the specification states: "Without wishing to be bound by theory, it is thought that the above interference problem may be as a result of PRP (with a low isoelectric point of less than 2) forming a strong interaction with aluminium hydroxide (with a high isoelectric point). This interaction may mask PRP epitopes from immune competent cells--particularly if the PRP/AlOH interaction forms a network of particles--a phenomenon called flocculation…."

Paragraph 0012 of the specification states that the polyanionic polymer of the present invention protects PRP in the vaccine "…for example by reducing the amount or rate of binding of PRP to adjuvant and/or the extent or rate of flocculation…."

The specification (both priority and PCT) states that 200 μM PLG was selected for clinical formulation for several reasons, including that "close to 80% PRP-T was non-adsorbed (according to the Dionex[1] test)" (Paragraph 0092). Paragraph 0095 states that "2000 μM PLG (Mw 1043--8 residues) could keep 80% of PRP-T in the supernatant (10 μg PRP/dose, 500 μg AlOH) with no flocculation resulting."

However, text added to the specification at the time of PCT filing (see "Maintenance of Adsorption of Antigens on Aluminium Hydroxide", starting at paragraph 0100) states that "(i)nterestingly in this experiment Hib [PRP] seems to be fully adsorbed onto the adjuvant but the PLG still prevents flocculation events (and Hib immune interference) from occurring". Applicant's representative reviewed the laboratory notebooks associated with this experiment, and determined that this added text is based on results from an ELISA assay, not a Dionex assay. Whereas ELISA uses PRP-specific antibodies, Dionex detects saccharides generally and is not specific for PRP.

Additionally, at paragraph 0095, statements are made about the ability of low and high molecular weight (Mw) PLG, respectively, to limit adsorption of PRP, and indicate that such results are measurable by ELISA or Dionex. As is discussed above, however, ELISA and Dionex techniques did not give comparable data regarding the amount of PRP in the supernatant.

[1] Dionex is an ion-exchange chromatography technique.

While not believing that the effect of PLG on the adsorption of PRP to adjuvant is material to the patentability of the present claim to an immunogenic composition, out of an abundance of caution Applicants wish to bring this issue to the Examiner's attention.

Respectfully submitted,

/Virginia Campen/

Virginia Campen
Attorney for Applicant
Registration No. 37,092

Date: June 7, 2011
GlaxoSmithKline
Global Patents
Five Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709-3398
Phone: 919-483-1012
Facsimile: 919-483-7977